REMARKS

Status of the Prosecution

Claims 45, 55-60, 63-65, 70-78, and 80 are pending and were examined. The objection to claim 45 was withdrawn. The rejection of claims 45, 55-58, and 70-78 under 35 U.S.C. §103(a) as allegedly unpatentable over any one of (1) Srivastava et al. (1997, Carcinogenesis 18: 1799-1808); (2) Russo et al. (1990, J. Natl. Cancer Inst. 82: 1286-1289); or (3) Russo et al. (1990, Br. J. Cancer 62: 2343-2347) was withdrawn.

Claims 45, 55-58, 60, 63, 64 and 70-76 stand finally rejected under 35 U.S.C. §103(a) as allegedly unpatentable over any one of (1) Srivastava et al. (1997), (2) Russo et al. (1990, J. Natl. Cancer Inst. 82: 1286-1289); or (3) Russo et al. (1990, Br. J. Cancer 62: 2343-2347) in view of Grattarola (1976, J. Natl. Cancer Inst. 56: 11-16).

Claims 45, 55-58, 59, 60, 63, 64 and 70-76 stand finally rejected under 35 U.S.C. §103(a) as allegedly unpatentable over any one of (1) Srivastava et al. (1997); (2) Russo et al. (1990, J. Natl. Cancer Inst. 82: 1286-1289); or (3) Russo et al. (1990, Br. J. Cancer 62: 2343-2347) in view of Grattarola (1976, J. Natl. Cancer Inst. 56: 11-16), and further in view of Silverstein et al. (1994, Cancer 73: 1673-1677, abstract only).

Claims 45, 55-58, 60, 63, 64, 65, and 70-76 stand finally rejected under 35 U.S.C. §103(a) as allegedly unpatentable over any one of (1) Srivastava et al. (1997); (2) Russo et al. (1990, J. Natl. Cancer Inst. 82: 1286-1289); or (3) Russo et al. (1990, Br. J. Cancer 62: 2343-2347), in view of Grattarola (1976, J. Natl. Cancer Inst. 56: 11-16), and further in view of Mgbonyebi et al. (1997, Proc. Ann. Meeting Am. Soc. Cancer Res. pp A1977 XP002109660).

Claims 45, 55-58, 60, 63, 64, 70-76, and 77 stand finally rejected under 35 U.S.C. §103(a) as allegedly unpatentable over any one of (1) Srivastava et al. (1997); (2) Russo et al. (1990, J. Natl. Cancer Inst. 82: 1286-1289); or (3) Russo et al. (1990, Br. J. Cancer 62: 2343-2347), in view of Grattarola (1976, J. Natl. Cancer Inst. 56: 11-16), and further in view of Saal et al. (1991 Fert. Steril. 56:225-9).

Claims 45, 55-58, 60, 63, 64, 70-76, and 78 stand finally rejected under 35 U.S.C. §103(a) as allegedly unpatentable over any one of (1) Srivastava et al. (1997); (2) Russo et al. (1990, J. Natl. Cancer Inst. 82: 1286-1289); or (3) Russo et al. (1990, Br. J. Cancer 62: 2343-

2347), in view of Grattarola (1976, J. Natl. Cancer Inst. 56: 11-16), and further in view of any one of (1) Platanias et al. (1998, J. Biol. Chem. 273: 5577-5581); (2) Oberg et al. (1989, J. Natl. Cancer Inst. 81: 531-535); (3) Recchia et al. (1998, Clin. Ter. 149: 203-208) or (4) Robinson et al. (1990, Breast Cancer Res. Treat. 15: 95-101).

Claims 45, 55-58, 60, 63, 64, 70-76, and 80 stand finally rejected under 35 U.S.C. §103(a) as allegedly unpatentable over any one of (1) Srivastava et al. (1997); (2) Russo et al. (1990, J. Natl. Cancer Inst. 82: 1286-1289); or (3) Russo et al. (1990, Br. J. Cancer 62: 2343-2347), in view of Grattarola (1976, J. Natl. Cancer Inst. 56: 11-16), and further in view of the Sigma Chemical Co. catalog (1995, page 263).

A Notice of Appeal was timely filed and received by the U.S. Patent and Trademark Office on January 3, 2006. This Amendment and Request for Reconsideration is filed together with a Request for Continued Examination, in lieu of an Appeal Brief.

Claims 55-60 are canceled herein without prejudice. Claim 45 is amended herein to more clearly define the method of the invention as a treatment for metastatic mammary tumors in postmenopausal women. No new matter has been added by way of these amendments. Applicants respectfully submit that the presently amended claims are in condition for allowance, for the reasons set forth below.

The Claims are Directed to Non-Obvious Subject Matter

Claims 45, 55-58, 60, 63, 64 and 70-76 are rejected under 35 U.S.C. §103(a) as allegedly obvious over any one of (1) Srivastava et al. (1997, Carcinogenesis 18: 1799-1808); (2) Russo et al. (1990, J. Natl. Cancer Inst. 82: 1286-1289); or (3) Russo et al. (1990, Br. J. Cancer 62: 2343-2347) in view of Grattarola (1976, J. Natl. Cancer Inst. 56: 11-16). The Office Action alleges that, although the primary references do not teach treatment of mammary tumors in postmenopausal women, the primary references do teach that hCG has a protective effect against breast cancer and Grattarola teaches a method of administering 15,000 IU hCG to advanced breast cancer patients who are pre- or postmenopausal women and had undergone surgery. According to the examiner, it therefore would have been obvious to combine the teachings of Grattarola with the primary references to arrive at the

invention as claimed. Applicants traverse the rejection as applied to the presently amended claims.

In order for a *prima facie* case of obviousness to be established under 35 U.S.C. §103, there must be a motivation in the art to modify or combine the references identified by the examiner, there must be a reasonable expectation of success, not merely an invitation to experiment, and the prior art references must teach or suggest all limitations of the claims. Moreover, the mere fact the references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. (MPEP 2143.01).

Claim 45 now calls for a method of treating metastatic mammary tumors in postmenopausal women. As the skilled artisan appreciates, metastatic mammary tumor is the most advanced and severe stage of breast cancer that calls for treatment regimens and therapeutic agents that may not be appropriate for other types of breast cancer (*see* excerpt from the Merck Manual Online (2006), Sec. 18, Chapter 242, attached hereto, particularly at page 8 of 10). The discovery, in accordance with the present invention, that hCG has a beneficial effect on metastatic breast cancer could not have been foreshadowed by the teachings of the cited references, alone or combined.

First, with respect to the three primary references, none of those references provides any hint that hCG could be effective in the treatment of metastatic mammary tumors in postmenopausal women. Indeed, each of the three cited references discloses a similar experimental protocol (set forth in Fig. 1 of Srivastava et al.; in Fig. 1 of Russo et al. 1990(1) and at 2344 (Materials & Methods) of Russo et al. 1990(2). The protocol calls for: (a) injecting 45 or 50 day-old virgin Sprague-Dawley rats with DMBA (or saline); and (b) 20 or 21 days later, injecting the rats with hCG (or saline) periodically for an ensuing number of days. Thus, in each protocol, only 20 or 21 days elapsed between treatment with the carcinogen and administration of the first dose of hCG. In no instance do any of the three references disclose that the rats had any tumors, let alone metastatic tumors, at the initiation of hCG treatment. On the contrary, Russo et al. 1990(2) (page 2344, right col., last paragraph and Fig. 1) specifically disclose that animals did not begin developing palpable tumors until six weeks after DMBA injection. Likewise, Russo et al. 1990(1) (Table 1) report a latency

period for tumor development in the DMBA + hCG (21 days later) (Group IV) of 49-154 days. Similarly, Srivastava et al. report that the earliest finding of a mammary tumor following DMBA administration was at 70 days of age (one animal out of 32 had a tumor). At best, then, each of the primary references teaches that hCG may prevent or delay the onset of mammary tumors in a subject exposed to a carcinogen, but they in no way suggest that hCG might be beneficial in the treatment of pre-existing tumors.

Since the primary references in no way teach or suggest that hCG would be effective in the treatment of postmenopausal women having metastatic mammary tumors, and each indeed specifically states that palpable tumors were not present at the time hCG treatment was initiated, none of the primary references, alone or combined, can be said to teach the invention as presently claimed.

Likewise, Grattarola nowhere teaches or suggests a method of treating metastatic mammary tumors in postmenpausal women by administering hCG to a woman having metastatic mammary tumors. In fact, the only hCG "treatment" mentioned by Grattarola at all was not even a treatment for mammary tumors – it was instead a means of confirming that the increased testosterone excretion observed in some women following ovariectomy (as an adjunct to mastectomy) was due to gonadotropins (see, e.g., page 11, right col., second full paragraph; left column, second full paragraph *et seq.*). Moreover, it should be noted that Grattarola *nowhere* teaches or suggests the use of hCG to treat mammary tumors, whether metastatic or not. Grattarola discloses a preferred treatment for breast cancer that comprises ovariectomy (as an adjunct to mastectomy), combined with corticosteroids (see, e.g., page 15, right col., first full paragraph). Hence, Grattarola cannot be said to teach the present invention, and indeed teaches away from the invention by teaching a substantially different regimen for treating breast cancer.

Thus, all of the limitations of the claimed invention are neither taught nor suggested by the cited references, alone or in combination. Accordingly, the skilled artisan would not be motivated to modify or combine the teachings of any of these references to arrive at the invention as claimed. Since the references fail to supply the motivation to make the invention as claimed, clearly the references also supply no expectation of success in practicing the

claimed invention. Accordingly, the cited references fail to establish a *prima facie* case of obviousness of the invention, and withdrawal of the rejection is therefore requested..

Claims 45, 55-58, 59, and 70-76 are rejected under 35 U.S.C. §103(a) as allegedly obvious over any one of (1) Srivastava et al. (1997); (2) Russo et al. (1990, J. Natl. Cancer Inst. 82: 1286-1289); or (3) Russo et al. (1990, Br. J. Cancer 62: 2343-2347) in view of Grattarola (1976, J. Natl. Cancer Inst. 56: 11-16), and further in view of Silverstein et al. (1994, Cancer 73: 1673-1677, abstract only). The Office Action alleges that although the primary references do not teach or suggest that hCG is effective as a treatment against tubular or lobular mammary carcinoma, Silverstein teaches that tubular or lobular invasive breast mammary carcinoma are forms of breast cancer, and that it would have been obvious to use the methods of the present invention to treat patients with these specific stages of the disease. Applicants traverse the rejection. All claims directed toward tubular or lobular mammary carcinoma have been canceled, thereby rendering this rejection moot. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection.

Claims 45, 55-58, 60, 63, 64, 65, and 70-76 stand finally rejected under 35 U.S.C. §103(a) as allegedly unpatentable over any one of (1) Srivastava et al. (1997); (2) Russo et al. (1990, J. Natl. Cancer Inst. 82: 1286-1289); or (3) Russo et al. (1990, Br. J. Cancer 62: 2343-2347), in view of Grattarola (1976, J. Natl. Cancer Inst. 56: 11-16), and further in view of Mgbonyebi et al. (1997, Proc. Ann. Meeting Am. Soc. Cancer Res. pp A1977 XP002109660).

The Office Action alleges that although the primary references do not teach or suggest that hCG is effective as a treatment for estrogen positive mammary tumors, Mgbonyebi teaches that hCG is effective in inhibition of estrogen positive breast cancer cells, and that it would have been obvious to use the methods of the present invention to treat patients with estrogen positive breast cancer cells. Applicants traverse the rejection.

The claims have been amended to recite that hCG is administered to a postmenopausal woman having metastatic mammary tumors. As explained above, neither of the primary references nor Grattarola teaches or suggests the use of hCG to treat patients having metastatic mammary tumors. Mgbonyebi et al., in teaching that that hCG inhibits growth of estrogen-positive breast cancer cells, does not supply the teaching that is clearly

absent from the primary references, that is, to use hCG to treat patients having metastatic mammary tumors. Again then, there is no suggestion in the cited references, alone or combined, to modify their teachings to arrive at the invention as presently claimed. Since the references fail to supply the motivation to make the invention as claimed, clearly the references also supply no expectation of success in practicing the claimed invention. Accordingly, the cited references fail to establish a *prima facie* case of obviousness of the invention, and withdrawal of the rejection is therefore requested.

Claims 45, 55-58, 60, 63, 64, 70-76, and 77 stand finally rejected under 35 U.S.C. §103(a) as allegedly unpatentable over any one of (1) Srivastava et al. (1997); (2) Russo et al. (1990, J. Natl. Cancer Inst. 82: 1286-1289); or (3) Russo et al. (1990, Br. J. Cancer 62: 2343-2347), in view of Grattarola (1976, J. Natl. Cancer Inst. 56: 11-16), and further in view of Saal et al. (1991 Fert. Steril. 56:225-9). The Office Action alleges that although the primary references do not teach or suggest injecting hCG subcutaneously, Saal teaches the administration of hCG subcutaneously, and that it would have been obvious to administer hCG subcutaneously in the methods of the present invention. Applicants traverse the rejection.

As set forth above, the present invention is directed to a method of treating metastatic mammary tumors in postmenopausal women, and the primary references do not teach or suggest this method. The deficiencies in the primary references are not supplied by Saal. Saal nowhere teaches or suggests that hCG could be administered subcutaneously to treat metastatic mammary tumors in postmenopausal women. So again, there is no suggestion in the cited references, alone or combined, to modify their teachings to arrive at the invention as presently claimed. Since the references fail to supply the motivation to make the invention as claimed, clearly the references also supply no expectation of success in practicing the claimed invention. Accordingly, the cited references fail to establish a *prima facie* case of obviousness of the invention, and withdrawal of the rejection is therefore requested.

Claims 45, 55-58, 60, 63, 64, 70-76, and 78 stand finally rejected under 35 U.S.C. §103(a) as allegedly unpatentable over any one of (1) Srivastava et al. (1997); (2) Russo et al. (1990, J. Natl. Cancer Inst. 82: 1286-1289); or (3) Russo et al. (1990, Br. J. Cancer 62: 2343-2347), in view of Grattarola (1976, J. Natl. Cancer Inst. 56: 11-16), and further in view of any

one of (1) Platanias et al. (1998, J. Biol. Chem. 273: 5577-5581); (2) Oberg et al. (1989, J. Natl. Cancer Inst. 81: 531-535); (3) Recchia et al. (1998, Clin. Ter. 149: 203-208) or (4) Robinson et al. (1990, Breast Cancer Res. Treat. 15: 95-101). The Office Action alleges that although the primary references do not teach hCG treatment in combination with Type 1 interferon, any one of Plantanias, Oberg, Recchia, or Robinson teach that Type 1 interferon has anti-tumor activity, and that it would have been obvious to use Type 1 interferon in combination with hCG. Applicants traverse the rejection.

As set forth above, the present invention is directed to a method of treating metastatic mammary tumors in postmenopausal women, and the primary references do not teach or suggest this method. The deficiencies in the primary references are not supplied by Plantanias, Oberg, Recchia, or Robinson because none of those references teach that hCG could be used in combination with Type 1 interferon to treat metastatic mammary tumors in postmenopausal women. Again then, there is no suggestion in the cited references, alone or combined, to modify their teachings to arrive at the invention as presently claimed. Since the references fail to supply the motivation to make the invention as claimed, clearly the references also supply no expectation of success in practicing the claimed invention. Accordingly, the cited references fail to establish a *prima facie* case of obviousness of the invention, and withdrawal of the rejection is therefore requested.

Claims 45, 55-58, 60, 63, 64, 70-76, and 80 stand finally rejected under 35 U.S.C. §103(a) as allegedly unpatentable over any one of (1) Srivastava et al. (1997); (2) Russo et al. (1990, J. Natl. Cancer Inst. 82: 1286-1289); or (3) Russo et al. (1990, Br. J. Cancer 62: 2343-2347), in view of Grattarola (1976, J. Natl. Cancer Inst. 56: 11-16), and further in view of the Sigma Chemical Co. catalog (1995, page 263). The Office Action alleges that although the primary references do not teach that the hCG used is recombinant, recombinant hCG is available through commercial suppliers such as Sigma Chemical Co., and that it would have been obvious to vary the presently claimed methods by using recombinant hCG. Applicants traverse the rejection.

As set forth above, the present invention is directed to a method of treating metastatic mammary tumors in postmenopausal women, and the primary references do not teach or suggest this method. The deficiencies in the primary references are not supplied by the

Sigma Chemical Co. catalog (1995, page 263). The Sigma Chemical Co. catalog (1995, page 263) does not teach or suggest that recombinant hCG could be administered in a method to treat metastatic mammary tumors in postmenopausal women. Again then, there is no suggestion in the cited references, alone or combined, to modify their teachings to arrive at the invention as presently claimed. Since the references fail to supply the motivation to make the invention as claimed, clearly the references also supply no expectation of success in practicing the claimed invention. Accordingly, the cited references fail to establish a *prima facie* case of obviousness of the invention, and withdrawal of the rejection is therefore requested.

Conclusion

In view of the amendments submitted herewith and the foregoing remarks, the presently pending claims are believed to be in condition for allowance. Applicants respectfully request early and favorable reconsideration and withdrawal of the objections and rejections set forth in the July 28, 2005 Official Action, and allowance of this application.

Respectfully submitted,

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Breast Cancer

The Merck Manual of Diagnosis and Therapy
Section 18. Gynecology And Obstetrics
Chapter 242. Breast Disorders
Topics
[General]
Benign Breast Disorders
Breast Cancer
Paget's Disease
Cystosarcoma Phyllodes
navigation help

(See also Chs. 142, 143, and 144.)

In situ carcinoma is contained entirely within the breast duct, with no invasion of adjacent normal tissues. Once fairly uncommon, it now accounts for > 15% of all breast cancers diagnosed in the USA, and the proportion is much higher in younger age groups. This increase is the result of better screening.

Ductal carcinoma in situ (DCIS) accounts for 43% of breast cancers diagnosed in women aged 40 to 49 and 92% of cases diagnosed in women aged 30 to 39. DCIS occurs in premenopausal and postmenopausal women, forms a palpable mass, and is more commonly localized to one quadrant of a breast. DCIS is frequently the cause of microcalcifications seen on mammograms. Patients are likely to develop an invasive cancer if they are not treated. DCIS is considered a precursor of invasive cancer, but because it is localized, it can be totally removed surgically.

Lobular carcinoma in situ (LCIS), or lobular neoplasia, occurs predominantly in premenopausal women and is usually found incidentally because it does not form a palpable mass. Microscopically, LCIS appears distinctly different from DCIS. Between 25 and 35% of patients with LCIS develop invasive breast cancer after a latency of up to 40 yr These invasive cancers occur with equal frequency bilaterally. Many specialists link LCIS with atypical hyperplasia, considering it indicative of a propensity for breast cancer rather than a true precursor.

Invasive ductal and lobular tumors are the most common histologic types of invasive cancer (about 90%). Patients with less common histologic types (eg, medullary or tubular lesions) have a somewhat better prognosis.

Risk Factors

In the USA, the cumulative risk of developing breast cancer is 12.64% (1 in 8) by age 95, and risk of dying of the disease is about 3.6%. Much of this risk is incurred after age 75 (see Table 242-1). These statistics can be misleading because the cumulative risk for the disease in any 20-yr period is considerably lower.

A **family history** of breast cancer in a first-degree relative (parent, sibling, child) doubles

or triples a woman's risk of developing the disease, but a history in more distant relatives increases the risk only slightly. In some studies, the risk was higher in women with relative who had bilateral breast cancer or whose cancer was diagnosed before menopause. When two or more first-degree relatives have breast cancer, the risk may be 5 to 6 times higher. About 5% of women with breast cancer carry one of the two breast cancer genes, *BRCA1* o *BRCA2*. If a relative of such women also carries the gene, she has an increased risk of developing breast cancer. Men who carry *BRCA2* also have an increased risk of developing breast cancer. The magnitude of risk is still uncertain but may be as high as 50 to 85% by age 80. However, women with *BRCA1* or *BRCA2* do not appear to have a greater risk of dying of breast cancer after it is diagnosed than women without the gene. Women with *BRCA1* have a similarly high risk of developing ovarian cancer. Women who do not have a family history of breast cancer in at least two first-degree relatives probably do not carry this gene. For this reason, most professional organizations discourage widespread screening for *BRCA1* and *BRCA2*.

Women with a **history of in situ or of invasive breast cancer** are another high-risk group. The risk of developing cancer in the contralateral breast after mastectomy is about 0.5 to 1.0%/yr.

Women with **early menarche, late menopause,** or a **late first pregnancy** are at increased risk. Women with a first pregnancy after age 30 are at higher risk than those who are nulliparous.

A **history of fibrocystic complex** increases risk, but this condition is an imprecise histologic diagnosis, often assigned when a breast biopsy reveals a few cysts with normal breast tissue or very minimal proliferation; therefore, the diagnosis has little meaning. Among women who have had a biopsy for a benign breast disorder, the increased risk appears to be limited to those with ductal proliferation, and even then, the risk is moderate except for women with atypical hyperplasia. For those with atypical hyperplasia and a positive family history in a first-degree relative, the risk is increased nearly ninefold. Women with multiple breast lumps but no histologic confirmation of a high-risk pattern should not be considered at high risk.

Women who use **oral contraceptives** have a very small increase in their risk of developing breast cancer; about 5 more cases of breast cancer per 100,000 occur among women who use oral contraceptives. The increased risk occurs primarily during the years when women are taking the contraceptives and tapers off during the 10-yr period after they stop. The risk is also related to the age at which contraceptives are begun. Women who begin to use contraceptives before age 20 have the greatest proportional increase in the risk of developing breast cancer, although this risk is still very low.

Similarly, the use of postmenopausal **estrogen replacement therapy** appears to increase the risk modestly, especially after 10 to 20 yr of use (see also Ch. 236). However, even with prolonged use, the risk is increased less than twofold. Use of a cyclic or continuous estrogen-progestin regimen also results in a modest increase in the risk of breast cancer. Selective estrogen-receptor modulators may be able to prevent heart disease and osteoporosis and treat hot flushes with no effect on the breast.

Environmental factors, such as **diet,** may play a role in causing or promoting the growth of breast cancers, but conclusive evidence about the effect of a particular diet (eg, one high in fats) is lacking. Obese postmenopausal women are at increased risk, but no evidence shows

that dietary modification decreases this risk. For obese women who are still menstruating, risk may be decreased.

Radiation exposure before age 30 also increases risk.

Symptoms, Signs, and Diagnosis

More than 80% of breast cancers are discovered as a lump by the patient. Less commonly, patients present with a history of pain and no mass, with breast enlargement, or with a nondescript thickening in the breast. A typical finding during physical examination is a dominant mass--a lump distinctly different from the surrounding breast tissue. Diffuse fibrotic changes in a quadrant of the breast, usually the upper outer quadrant, are more characteristic of benign disorders, but a slightly firmer thickening not noted in the contralateral breast may be a sign of cancer. More advanced breast cancers are characterized by fixation of the mass to the chest wall or to overlying skin, by the presence of satellite nodules or ulcers in the skin, or by exaggeration of the usual skin markings resulting from lymphedema (peau d'orange). If matted or fixed axillary lymph nodes and/or supraclavicular or infraclavicular lymphadenopathy is present, surgery is unlikely to be curative. Inflammatory breast cancer is particularly virulent, characterized by diffuse inflammation and enlargement of the breast, often without a mass.

If cancer is suspected during physical examination, biopsy should be planned. A prebiopsy mammogram may help delineate other areas of the breast that should be biopsied and serves as a baseline for future reference. However, mammogram results should not alter the decision to perform a biopsy.

Fine-needle aspiration and cytologic evaluation may be sufficient to confirm cancer but should be performed only by those experienced in the technique. If aspirate from a suspicious lesion is negative, a more definitive procedure should be performed: needle or incisional biopsy or, if the tumor is small, excisional biopsy. Increasingly, stereotactic biopsies (a needle biopsy performed during mammography) are being used to improve diagnostic accuracy. Evidence indicates that this method is at least as accurate and as safe as traditional biopsy methods. Most biopsies can be performed using a local anesthetic. The excised specimen may be placed in India ink before sectioning so that normal tissue margins surrounding the tumor can be defined more precisely.

Part of the biopsy specimen should be routinely analyzed for estrogen and progesterone receptors. These cytoplasmic proteins can be measured by a steroid-binding assay, which requires about 1 g of fresh tumor pulverized to form a crude tumor cell homogenate, or by estrogen-receptor immunochemical assay (ER-ICA), which requires less fresh tissue. ER-ICA performed with fixed tissue sections is less reliable. About 2/3 of patients have an estrogen-receptor positive (ER+) tumor; the incidence of ER+ tumors is greater among postmenopausal than among premenopausal women. Patients with estrogen receptors have a somewhat better prognosis and are more likely to benefit from endocrine therapy. A progesterone receptor on the tumor is thought to reflect a functional estrogen receptor. The presence of estrogen and progesterone receptors predicts a greater likelihood of response than the presence of estrogen receptors alone. Knowledge of receptor status at the time of diagnosis may be useful in the selection of adjuvant therapy (after excision or radiation therapy) and palliative therapy if metastatic disease develops.

Tumor tissue specimens may be evaluated for ploidy and S-phase fraction of cells. Patients who have aneuploid tumors or tumors with a high percentage of cells in S phase have a worse prognosis. These tests are performed at many commercial laboratories, but standardized values to identify a poor prognosis and quality control programs to ensure the comparability of results from different laboratories have not been established. Eventually, these tests may help determine prognosis in patients without histologic involvement of axillary lymph nodes.

Treatment can be delayed for one to several weeks after biopsy so that a thorough evaluation for metastatic disease can be performed. Minimally, it should include a physical examination for lymphadenopathy, skin metastases, and hepatomegaly; a chest x-ray; liver function studies; and a CBC. Carcinoembryonic antigen (CEA) and cancer antigen 15-3 are elevated in > 50% of patients with metastatic disease. A bone scan should be obtained routinely for patients with larger tumors or lymphadenopathy. Bone scans are rarely positive in patients without lymphadenopathy whose tumors are < 2 cm in diameter. However, they provide a valuable baseline if signs of metastatic disease (eg, musculoskeletal pain) develop. Liver scans are rarely positive in patients with normal liver function studies, normal CEA, and no evidence of hepatomegaly during physical examination.

Screening

Breast examination by patient or physician begins with visual inspection for asymmetry in breast size, nipple inversion, bulging, or dimpling. Fig. 242-1 A and B shows the usual positions for such inspection. An underlying cancer is sometimes detected by having the patient press both hands against the hips or the palms together in front of the forehead (see Fig. 242-1 C and D). In these positions, the pectoral muscles are contracted, and a subtle dimpling of the skin may appear if a growing tumor has entrapped a Cooper's ligament. The axillary and supraclavicular lymph nodes are most easily examined while the patient is seated or standing (see Fig. 242-1 E). Supporting the patient's arm during the axillary examination allows the arm to be fully relaxed so that nodes deep within the axilla can be palpated. Although examination of the breast with the patient seated may disclose a lesion not palpated in any other way, a more systematic examination should be performed with the patient supine, the ipsilateral arm raised above her head, and a pillow under the shoulder ipsilateral to the breast being examined (see Fig. 242-1 F). This position is also used for breast self-examination; the patient examines the breast with her contralateral hand.

The breast should be palpated with the palmar surfaces of the second, third, and fourth fingers, moving systematically in a small circular pattern from the nipple to the outer edges (see Fig. 242-1 G). The precise location and size (measured with a caliper) of any abnormality should be noted on a drawing of the breast, which becomes part of the patient's record. A written description of the consistency of the abnormality and the degree to which it can be distinguished from surrounding breast tissue should also be included. The record should indicate whether the abnormality was considered benign or potentially malignant, because the presence of abnormalities during physical examination should be the major determinant in deciding whether to perform a biopsy, even if a subsequent mammogram does not show the suspicious area.

The patient should be instructed in breast self-examination during her annual breast examination by a physician or a specially trained nurse. The patient should perform these

examinations monthly. Routine self-examination has not been proved to reduce breast cancer mortality nor to be as beneficial as routine mammographic screening; however, tumors found with this technique are usually smaller, are associated with a better prognosis and are more easily treated with breast-conserving surgery (see below).

Routine mammography reduces breast cancer mortality by 25 to 35% in asymptomatic women >= 50 yr and probably by a smaller percentage in asymptomatic women < 50 yr. In screening studies, about 40% of the cancers were detected by mammography but not by physical examination. Mammography for women > 50 yr should be performed yearly. However, there is considerable disagreement about screening in women 40 to 50 yr. Recommendations for this age group include annual mammography (The American Cancer Society), mammography every 1 to 2 yr (The National Cancer Institute), and no periodic mammography (The American College of Physicians, which considers the benefits of mammography for this age group to be uncertain).

Signs of early breast cancer detected by mammography include microcalcifications, subtle distortions of breast architecture, and crablike lesions that cannot be palpated. However, these abnormalities are not always found in patients who present with a mass or other suggestive signs, and the incidence of false-negative results may exceed 15%, depending partly on the techniques used and the experience of the mammographer. Suspicious areas on a mammogram that cannot be detected during physical examination may be localized by inserting two needles or wires using radiologic guidance, so that a biopsy of the lesion can be performed. The specimen should be x-rayed, and the x-ray compared with the prebiopsy mammogram to ensure that the suspicious area has been removed. Mammography is repeated when the breast is no longer tender, usually 6 to 12 wk after the biopsy, to confirm removal of the suspicious area.

Ultrasonography helps distinguish a breast cyst from a solid mass. A cyst usually requires no treatment if the patient is asymptomatic (although some physicians believe all cysts should be aspirated and the fluid sent for cytologic studies), whereas a mass usually requires biopsy. Ultrasonography is not used in routine screening for cancer. Because **thermography** and **diaphanography** (transillumination) have very high false-positive and false-negative rates, they are not useful for screening.

Primary Treatment

Invasive cancer: Survival rates for patients treated with modified radical mastectomy (simple mastectomy plus lymph node dissection) and for patients treated with breast-conserving surgery (lumpectomy, wide excision, partial mastectomy, or quadrantectomy) plus radiation therapy appear to be identical, at least for the first 20 yr. Patient preference plays a major role in the choice of treatment. The primary advantage of breast-conserving surgery with radiation therapy is cosmetic, with its resulting sense of body integrity. However, this advantage may not exist if the tumor is large in relation to the breast, because total removal of the tumor mass with a tumor-free margin of normal tissue is necessary for long-term control of breast cancer. Some physicians use preoperative chemotherapy to shrink the tumor before removing the lump and applying radiation therapy. Early data suggest that this approach does not compromise survival and may enable some women to choose breast-conserving surgery instead of mastectomy.

For about 15% of patients treated with breast-conserving surgery and radiation therapy,

distinguishing the treated breast is difficult. More often, however, the treated breast shrinks some, and some thickening or disruption of contour may occur in the area of the wide excision. These changes can be minimized by attention to cosmetic detail during the initial biopsy and during reexcision if it becomes necessary. Other adverse effects of radiation therapy are usually transient and mild; they include erythema or painless blistering of the skin during therapy, mild pneumonitis 3 to 6 mo after completing therapy in about 10 to 20% of patients, and asymptomatic rib fractures in < 5%.

Most invasive tumors have one or more small areas of intraductal (in situ) cancer; in some studies, tumors with an extensive (> 25%) intraductal component (EIC+) within the invasive tumor area and in nearby tissue had a high recurrence rate within the breast after breast-conserving surgery and radiation therapy. However, distant recurrence rates and survival rates after breast-conserving surgery are the same whether the tumor was EIC+ or EIC-. Local control of EIC+ tumors is best achieved by mastectomy or a reexcision of the original tumorous area to rule out multiple foci of remaining tumor.

The modified radical mastectomy removes all breast tissue but preserves the greater pectoral muscle and eliminates the need for skin graft; it has replaced the Halsted's radical mastectomy. Survival time after modified radical mastectomy and that after radical mastectomy are equivalent, and breast reconstruction is considerably easier after modified radical mastectomy. Radiation therapy administered as an adjuvant after mastectomy significantly reduces the incidence of local recurrence on the chest wall and in the regional lymph nodes but does not improve overall survival time. Consequently, radiation therapy after mastectomy is being used less often.

Procedures for reconstruction include placement of a submuscular or, less commonly, a subcutaneous silicone or saline implant; use of a tissue expander with delayed placement of the implant; transference of muscle and blood supply from the latissimus dorsi or the lower rectus abdominis; and creation of a free flap by anastomosing the gluteus maximus to the internal mammary vessels. Choice of procedure depends on the extent of previous surgery or radiation therapy, the experience of the plastic surgeon, and the patient's willingness to undergo more extensive surgical procedures or experience muscle weakness in areas where muscles are removed. Reconstruction immediately after mastectomy requires prolonged anesthesia and coordination between the general and plastic surgeons.

A lymph node dissection or node sampling can be performed as part of a modified radical mastectomy or as a separate axillary incision during breast-conserving surgery. Morbidity is much less if node dissection is limited to the areas medial and inferior to the subclavian vessels. More extensive procedures are probably not justified because the main value of lymph node removal is diagnostic, not therapeutic.

Node status correlates with disease-free and overall survival better than any other prognostic factor. For node-negative patients, the 10-yr disease-free survival rate exceeds 70%, and the overall survival rate exceeds 80%. The rates are about 25 and 40%, respectively, for node-positive patients. The prognosis is worse with each additional positive lymph node found, but three classifications are traditionally used: node-negative, 1 to 3 positive nodes, and >= 4 positive nodes. For patients in the last group, the 10-yr disease-free survival rate is about 15%, and the overall survival rate is about 25%. Larger lesions are more likely to be node-positive. Size also has independent prognostic value; with each 1-cm increase in size, prognosis worsens. Some experts believe that a tumor < 1 cm indicates an excellent prognosis and that no adjuvant therapy is required, and some

believe that a tumor > 5 cm requires adjuvant systemic therapy before mastectomy or breast-conserving surgery. Patients with poorly differentiated tumors have a worse prognosis; however, different pathologists examining the same slides tend to judge them differently.

In situ carcinoma: LCIS is treated with close observation or with bilateral mastectomy. Most patients with DCIS are cured by simple mastectomy, which has been the standard treatment for this type of cancer. However, more patients are being treated with wide excision alone (especially if the lesion is < 2.5 cm and the histologic characteristics are favorable) or with wide excision plus radiation therapy when size and histologic characteristics are less favorable. Randomized studies show that the addition of radiation therapy decreases the chance that invasive breast cancer will develop for at least 5 to 10 yr after treatment. There is no evidence that radiation therapy improves survival, which exceeds 98 to 99% regardless of which treatment is used.

Inflammatory cancers: Initial treatment is systemic therapy, usually chemotherapy, followed by radiation therapy. Although about 2/3 of inflammatory breast cancers are ER+ the role of hormone therapy--alone or with chemotherapy--is not well defined.

Adjuvant Systemic Therapy

Chemotherapy or endocrine therapy, begun soon after the completion of primary therapy and continued for months or years, delays recurrence in almost all patients and prolongs survival in some.

Adjuvant chemotherapy decreases the annual odds of death by 25 to 35% in premenopausa node-positive women, at least during the first 15 yr of follow-up. At 10 yr, 10% more treated patients are alive, and the difference in median survival time for premenopausal node-positive patients treated with adjuvant chemotherapy is on average 1.5 to 3 yr longer than that for those treated with mastectomy alone. Chemotherapy also decreases the annual odds of death in premenopausal women who are at lower risk of recurrence (eg, those without lymph node involvement) by 25 to 35%. However, the absolute difference in survival at 10 yr is smaller (1 to 9%) than that in node-positive women. The effect of adjuvant chemotherapy in postmenopausal women is about half that in premenopausal women: a 9 to 19% reduction in the annual odds of death and a much smaller absolute benefit in survival at 10 yr. Postmenopausal women with ER- tumors benefit the most from adjuvant chemotherapy.

Combination chemotherapy regimens--such as cyclophosphamide, methotrexate, and 5-fluorouracil (CMF) or cyclophosphamide and doxorubicin (CA)--are more effective than a single drug. Regimens given for 4 to 6 mo, which are as effective as regimens given for 6 t 24 mo, are most effective. Acute adverse effects depend on the regimen used but usually include nausea, infrequent vomiting, mucositis, easy fatigability, mild to severe alopecia, myelosuppression, and thrombocytopenia. Long-term adverse effects occur infrequently with most regimens, and death from infection or bleeding is rare (< 0.2%).

Adjuvant tamoxifen therapy provides nearly the same benefits in women with ER+ tumors as chemotherapy does in premenopausal women. Adjuvant tamoxifen for 5 yr reduces the annual odds of death by about 25% in premenopausal and postmenopausal women and in women with or without axial lymph node involvement. The absolute increase in survival is

slightly less than 10% at 10 yr. Treatment for 5 yr is superior to that for 2 yr, but treatment for > 5 yr has no advantage. Tamoxifen has almost no acute adverse effects, especially in postmenopausal women, but it has antiestrogenic effects on breast tissue and estrogenic effects on other parts of the body. Thus, tamoxifen decreases the incidence of contralateral breast cancer (an antiestrogenic effect) and decreases serum cholesterol (an estrogenic effect). Tamoxifen therapy may reduce cardiovascular mortality and osteoporosis, but it significantly increases the risk of developing endometrial cancer. However, the improvement in survival from breast cancer far outweighs the increased risk of death from uterine cancer. Tamoxifen may cause depression in >= 10% of patients.

Some form of adjuvant chemotherapy (eg, CMF for 6 mo, CA for 4 mo) should be routinely given after mastectomy or after lumpectomy plus radiation therapy to all premenopausal node-positive patients. Tamoxifen may be used instead of chemotherapy in premenopausal women with ER+ tumors, especially those with low-risk tumors, but giving both tamoxifen and chemotherapy to premenopausal women has no demonstrated advantage. After local therapy, adjuvant tamoxifen should be routinely given for 5 yr to postmenopausal women with ER+ tumors. Adjuvant chemotherapy may be given to postmenopausal women with ER- tumors, and giving chemotherapy and tamoxifen to this group of women has a small benefit. However, whether adjuvant tamoxifen therapy should be given to patients likely to derive only a small benefit (eg, patients without lymph node involvement or postmenopausal women given chemotherapy) is controversial. Treatment with high doses of chemotherapy plus bone marrow transplantation, which is under study, is also controversial.

Treatment of Metastatic Disease

Breast cancer may metastasize to almost any organ in the body; most commonly, it metastasizes lungs, liver, bone, lymph nodes, and skin. Breast cancer is also a common cause of metastases to the CNS. About 10% of patients with metastases to bone eventually develop hypercalcemia. Most metastases to skin occur in the region of the breast surgery; metastases to the scalp are also common. Because metastases frequently appear years or decades after initial diagnosis and treatment of breast cancer, symptoms should prompt immediate evaluation.

Treatment of metastases increases median survival by 3 to 6 mo. Even relatively toxic therapies (eg, chemotherapy) palliate symptoms and improve quality of life. Choice of therapy depends on the hormone-receptor status of the primary tumor or metastatic lesion, the length of the disease-free interval (from diagnosis to presentation of metastases), the number of metastatic sites and organs affected, and the patient's menopausal status. Patient with one metastatic focus always have others, even if they are not immediately apparent after the initial relapse. Thus, most patients with metastatic disease are treated with systemic endocrine therapy or chemotherapy. However, patients with a long disease-free interval (eg, >= 2 yr) and a single metastatic site may not have signs of additional metastases for months or years; in such patients, radiation therapy alone may be used to treat isolated, symptomatic bone lesions or local skin recurrences not amenable to surgical resection. Radiation therapy is the most effective treatment for brain metastases, occasionally achieving long-term control. Patients with multiple metastatic sites outside the CNS should initially be given systemic therapy; radiation therapy is usually withheld until there is evidence that systemic treatment is inadequate. There is no proof that treatment of patients with asymptomatic metastases substantially increases survival.

Endocrine therapy is preferred over chemotherapy in patients with ER+ tumors, a disease-free interval of > 2 yr, or disease that is not life threatening. Endocrine therapy is especially effective in premenopausal women in their 40s and postmenopausal women who had their last menstrual period > 5 yr earlier. However, none of these factors should be the sole criterion for choosing endocrine therapy over chemotherapy. For example, a 70-yr-old woman with an ER- tumor, a disease-free interval of > 5 yr, and metastatic disease limited to several bones may be treated with endocrine therapy. Conversely, a 35-yr-old premenopausal woman with an ER+ tumor, a disease-free interval of 6 mo, and extensive liver involvement may be a candidate for chemotherapy.

The aromatase inhibitors (anastrazole, letrozole, exemestane) are increasingly the endocrin therapy used first for postmenopausal women because of their greater effectiveness and relative lack of toxicity. These drugs act by decreasing the availability of estrogen needed to maintain tumor growth. Aminoglutethimide, an older aromatase inhibitor that must be given with hydrocortisone, is rarely used. In premenopausal women, ovarian ablation by surgery, radiation therapy, or use of a luteinizing-releasing hormone antagonist, is an alternative. In premenopausal women, tamoxifen may be used first or after the patient has had a response to ovarian ablation. A patient who initially responds to endocrine therapy but whose disease progresses months or years later should be treated sequentially with additional forms of endocrine therapy for as long as the benefit continues. Tamoxifen may be used as a 2nd line endocrine therapy in postmenopausal women. Progestins (medroxyprogesterone or megestrol), almost as nontoxic as the aromatase inhibitors and tamoxifen, are also commonly used as 2nd or 3rd line therapy. Although estrogens and androgens are also effective, they are not used often because they produce more adverse effects than other endocrine therapies. For the same reason, adrenalectomy and hypophysectomy are rarely used.

The most effective cytotoxic drugs for the treatment of metastatic breast cancer are cyclophosphamide, doxorubicin, paclitaxel, docetaxel, navelbine, capecitabine, and mitomycin C. The response rate to a combination of drugs is higher than that to a single drug. Most patients requiring palliative treatment with combination chemotherapy are initially given cyclophosphamide, methotrexate, and 5-fluorouracil (CMF) or cyclophosphamide, doxorubicin, and 5-fluorouracil (CAF). Response rates to regimens including doxorubicin are higher than those to CMF, and doxorubicin regimens provide a small additional survival benefit. However, doxorubicin regimens are associated with more severe alopecia and cardiotoxicity. The administration of prednisone with CMF increases the response rate and decreases myelosuppression and GI toxicity, but prednisone increases the incidence of secondary infection and thromboembolic phenomena. No other combination (eg, a paclitaxel combination) has been shown to be superior to CAF. For patients refractory to cyclophosphamide and doxorubicin, palliation with a taxane, navelbine, mitomycin C, or vinblastine may be successful, but prolonged remissions are rarely induced.

The use of new drugs and treatment strategies, such as biologic response modifiers, must b considered early in the course of disease, before extensive chemotherapy has been given, if they are to be beneficial. Interferons, interleukin-2, lymphocyte-activated killer cells, tumo necrosis factors, and monoclonal antibodies do not yet have an established role in breast cancer therapy. However, monoclonal antibody to the receptor for the growth factor HER-2/*neu* (trastuzumab) can induce remission in patients with metastatic breast cancer and increase the value of cytotoxic therapy in some patients.

Treatment with high doses of chemotherapy and bone marrow transplantation is under study in patients with metastatic breast cancer. Some results are promising, but whether thi approach can substantially improve survival for women who do not respond to standard-dose chemotherapy is unclear.

End-of-life care: Once aggressive treatment becomes inappropriate, care should focus or relieving pain and suffering (see Ch. 294).

Breast Cancer in Men

The incidence of breast cancer in men is 1% of that in women. This cancer more often progresses to an advanced stage in men because the diagnosis is seldom suspected, but the prognosis for men is identical to that for women in the same stage. Treatment is also nearly identical, although breast-conserving surgery is rarely used and no firm data on the value o adjuvant therapy are available. Metastatic tumors respond to all of the endocrine therapies used to treat female breast cancer and to orchiectomy. For men with metastatic disease refractory to endocrine therapy, palliation with combination chemotherapy may be successful.